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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/099,818	GREWAL, IQBAL	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/07/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14,15,19,32,33,36-52 and 55-59* is/are pending in the application.

4a) Of the above claim(s) *19,40-45,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14,15,32,33,36-39,46-52 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/7/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 01/07/2009, has been entered.

Claims 1, 5, 15, 37-39, 52 and 55 have been amended.

Claims 56-59 have been added.

Claims 53-54 have been canceled.
Claims 9-13, 16-18 and 20-31 and 34-35 have been canceled previously.

Claims 1-8, 14-15, 19, 32-33, 36-52 and 55-59 are pending.

The following of record is reiterated for applicant's convenience.

Newly submitted claims 58-59 (like claims 40-45 previously submitted) are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Newly submitted claims 58-59 are drawn to methods of further administering a cytotoxic or chemotherapeutic agent previously not claimed.

The newly submitted claims encompass the administration of cytotoxic or chemotherapeutic agents that differ in structure and function from the combination of anti-CD40 antibodies / anti-CD20 antibodies previously elected in the claimed methods of treating a neoplastic disease or disorder.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Given these differences between the newly submitted cytotoxic and chemotherapeutic agents, the previous prosecution on methods employing CD40-specific antibodies and CD20-specific antibodies in the absence of cytoxotoxic and chemotherapeutic agents and the non-coextensive searches based upon such differences,

newly submitted claims 58-59 have been withdrawn from consideration as being drawn to the non-elected species based upon original presentation.

Therefore, given the above, including issues under the various patent statutes and how they would apply to methods versus product claims; one or more of the following reasons apply, as indicated in the previous Office Action:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph

The newly submitted claims would be subject to election of species.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claims 19, 40-45 and newly added claims 58-59 have been withdrawn from consideration as being directed to a non-elected invention or species. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03.

As pointed out previously, applicant's election of Group I and the species of a CD40-specific antibody and a CD20-specific antibody as well as multiple myeloma in the reply filed on 11/14/2005 has been acknowledged.

Also, consistent with the previous indication, claims 1-8, 14-15, 32-33, 36-39, 46-52 and 55-57 are under consideration in this application as they read on CD40-specific antibodies and CD20-specific antibodies as the specific agents as well as the various neoplastic diseases claimed in the interest of compact prosecution.

2. The text of those sections of Title 35 USC not included in this Office Action can be found in a prior Action.

This Office Action will be in response to applicant's amendment, filed 01/07/2009.

The rejections of record can be found in the previous Office Action, mailed 08/08/2008.

3. Upon reconsideration of applicant's amended claims, filed 01/07/2009, the previous rejection under 35 U.S.C. § 112, first paragraph, written description new matter has been withdrawn.

4. Upon reconsideration of applicant's amended / canceled claims, filed 01/07/2009, the previous rejection under 35 U.S.C. 112, first paragraph, written description has been withdrawn.

5. *This is a written description / not a new matter rejection.*

This is a New Grounds of Rejection.

Claims 56-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite and encompass anti-CD40 S2C6-specific antibodies which comprise substitutions in the CDRs as follows, which do not meet do not meet the written description provision of 35 USC 112, first paragraph.

Claim 56 (New): The method of claim 1, wherein the humanized antibody derived from S2C6 comprises three heavy chain complementarity determining regions and three light chain complementarity determining regions from S2C6, wherein one to five amino acids in the heavy or light chain complementarity determining regions are further substituted, and the humanized antibody maintains or improves the affinity of the humanized antibody without the substitutions.

Claim 57 (New): The method of claim 56, wherein one amino acid in the heavy chain complementarity determining regions is further substituted.

There is insufficient guidance and direction as to the written description of the claimed anti-CD40 antibodies comprising said substitutions.

Given the well known high level of polymorphism of immunoglobulins / antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention;
one of skill in the art would conclude that applicant was not in possession of the structural attributes of a representative number of species possessed by the members of the genus of anti-CD40 antibodies, broadly encompassed by the claimed invention.

One of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genera.

It has been well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. All of the heavy and light chain CDRs should be in their proper order and in the context of framework sequences which maintain their required conformation in order to provide a binding molecule having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979-1983 (1982).

Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Single amino changes to either a CDR or even in certain circumstances to the framework can result in decrease affinity of antigen or even ablation of antibody binding and specificity.

Also, see the teachings of Colman (Research in Immunology 145: 33-36, 1994) on the effects of amino acid sequence changes on antibody-antigen interactions.

In addition, Kussie et al. (J. Immunol. 152: 146-152, 1994) (e.g., see entire document, including Table I) teach that the substitution of a single amino acid can totally ablate antigen binding.

Further, Chen et al. (EMBO J., 14: 2784-2794, 1995) teach that the substitution of a single amino acid can totally ablate antigen and that the same substitution in closely related antibodies can have opposite effects binding (e.g., see entire document, including Figure I). For example, the authors compared the effects of identical substitutions in related antibodies DI6 and TI5, and as shown in Figure 3, some substitutions increased antigen binding in one antibody while ablating it in the other.

However, the instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genera of "substitutions, broadly encompassed by the claimed invention.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which residues are required for the antibody to have anti-CD40 binding specificities by claiming substitutions without reciting the appropriate substitutions, broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genus of S2C6-based anti-CD40 antibodies based upon only claiming substitutions without reciting the appropriate substitutions, broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

6. Claims 1-8, 14-15, 32-33, 36-39, 46-52 and 55-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegall et al. (U.S. Patent No. 6,843,989) (892; of record) in view of Li et al. (U.S. Patent No. 6,495,129), Hanna et al. (US 2001/0018041 A1) and Grillo-Lopez (U.S. Patent No. 6,455,043) (892; of record), Benoit et al. (Immunopharmacology 35: 129-139, 1996) (1449; #59).

Applicant's arguments, filed 01/07/2009, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant argues the following.

Claims in the present application recite a method for treating a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal by administering an anti-CD20antibody, and a CD40 specific binding agent that binds and stimulates CD40, enhances interaction between CD40 and CD40L and arrests the growth of or causes deletion of cells expressing CD40, which CD40 specific binding agent is a chimeric antibody or a humanized antibody derived from S2C6; wherein the CD20 specific binding agent and the CD40 specific binding agent in combination inhibits the neoplastic disease or disorder in the mammal. See claim 1. As noted in the previous response, in addition to delivering a stimulatory signal, antibody S2C6 enhances the interaction between CD40 and CD40L. See page 19, lines 29-33. The feature of enhancing the interaction between CD40 and CD40L is different from other anti-CD40 antibodies, such as M2, M3 and G28-5. See specification, page 19, lines 20-27; and WO 00/75348, page 54, lines 20-28.

Applicant respectfully submits that the references cited by the Examiner do not provide the teaching, suggestion, or motivation that would have led one of ordinary skill to modify the references or to combine the reference teachings to arrive at the claimed invention.

As noted by the Examiner, Siegall et al. (US 6,843,989) teaches methods of treating cancer with anti-CD40 antibodies including S2C6, but this reference does not teach or suggest the use of an anti-CD40 antibody in combination with an anti-CD20 antibody.

Li et al. does not provide further teaching or motivation to use an anti-CD20 antibody with an anti-CD40 antibody for treating a neoplastic disease or disorder. Li et al. teaches administration of a human myeloid progenitor inhibitory factor-1 (MPIF-1) with Rituximab or Rituximab with any combination of the components of CHOP. See col. 113, lines 57-61; and col. 147, paragraph 3. Li et al. also teaches administration of a human myeloid progenitor inhibitory factor-1 (MPIF-1) with a cytokine, such as an anti-CD40 agonist or antagonist antibody. See col. 113, lines 63-66; and col. 153, lines 12-18. This reference does not teach or suggest use of an anti-CD20 antibody in combination with an anti-CD40 antibody for treating a neoplastic disorder in a human patient.

Grillo-Lopez discloses treating various neoplastic disease or disorder with anti-CD20 antibodies. This reference does not teach or provide the motivation for a combination therapy with an anti-CD20 antibody and an anti-CD40 antibody having the characteristics of antibody S2C6.

Benoit et al. does not provide further motivation to combine a chimeric antibody or a humanized antibody derived from S2C6 with an anti-CD20 antibody in the treatment of a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal. The teachings of Benoit et al. are limited to a single anti-CD40 antibody which is produced by hybridoma G28.5. Data presented in Siegall et al. (US 6,843,989) showed antibody S2C6 enhanced CD40/CD40L interaction in in vitro studies. In contrast, under the same experimental conditions the antibody G28-5 either did not enhance or inhibited the interaction between CD40 and CD40L. See US 6,843,989, col. 30, line 47 to col. 31, line 34. The claims as amended are directed to an anti-CD40 antibody that binds and stimulates CD40 and enhances interaction between CD40 and CD40L.

Benoit et al. does not teach or suggest such as an antibody. Accordingly, one skilled in the art would not view that the teachings in Benoit et al. could be applied to presently claimed invention.

As discussed in the previous response, Hanna et al. do not provide the motivation to use a combination of an anti-CD20 antibody with an antibody having the characteristics of S2C6, i.e., enhancing the interaction between CD40L and CD40. Hanna et al. teaches away from using this combination. Example 3 in Hanna et al. showed that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody Rituxan®. See Table 1. The data in this Example indicates that activation of the CD40L-CD40 pathway by soluble CD40L (sCD40L) generated resistance of RITUXAN® induced apoptosis in DHL-4 lymphoma cells. In view of the data, one skilled in the art would not be motivated to use an anti-CD40 antibody (such as antibody S2C6) that enhances the interaction between CD40L and CD40 in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder.

In view of the teachings in Siegall, Li et al., Hanna et al., Grillo-Lopez, and Benoit et al., one skilled in the art would not be motivated to administer an anti-CD20 antibody with a chimeric antibody or a humanized antibody derived from antibody S2C6 for treating a neoplastic disease or disorder as claimed.

Although it is known in the art that certain drugs can be used in combination with another drug to enhance the treatment efficacy, it is also well known that it is not predictable which combination of drugs could achieve the enhanced therapeutic effects for a type of cancer in a patient. The references cited by the Examiner do not teach or suggest that the combination therapy with an antibody having characteristics of S2C6 and an anti-CD20 antibody would have an enhanced therapeutic effect in treating neoplastic disease or disorder. Applicant respectfully submits that the references do not provide reasonable expectation of success.

As discussed above and argued in the previous response, data in Hanna et al. indicates that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody, RITUXAN®. In view of this teaching, one skilled in the art would not expect an anti-CD40 antibody that enhances the interaction between CD40 and CD40L in combination with an anti-CD20 antibody would have a better effect in treating B-lymphoma as compared to use of each antibody alone. Benoit et al. only disclose that in an in vitro assay, combining antibody G28.5 (an anti-CD40 antibody) with an anti-CD20 antibody resulted in increased inhibition past that produced by the anti-CD40 antibody alone. Siegall et al. showed antibody G28-5 did not enhance and even inhibited the interaction between CD40 and CD40L, in contrast to the antibody S2C6 which enhanced CD40/CD40L interaction in in vitro studies. In view of the teachings in these references, one skilled in the art would not reasonably expect that an anti-CD40 antibody having characteristics of S2C6 in combination with an anti-CD20 antibody would have an enhanced effect in treating a neoplastic disorder or disease.

In addition, as argued in the previous response, the present application shows that the anti-CD20 antibody used in combination with anti-CD40 antibody S2C6 had more than cumulative effect in anti-tumor activity. Example I of the present application is based on the experiments using anti-CD40 antibody S2C6 and anti-CD20 antibody RITUXAN®. The data in Example I shows that "[s]urvival was extended in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody compared with control animals and animals receiving anti-CD40 antibody or anti-CD20 antibody alone." See Specification at page 46, lines 22 -25. This result was not merely a cumulative effect based upon the use of the anti-CD40 antibody and the anti-CD20 antibody. As shown in Figure 4, three out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD40 antibody while five out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD20 antibody.

In contrast, ten out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the combination of the anti-CD20 antibody and the anti-CD40 antibody. See Figure 4. Further, the "[t]umor volume in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody was significantly reduced compared to control animals and animals receiving anti-C40 antibody or anti-CD20 antibody alone." See Specification at page 46, lines 29-33. As shown in Figure 5, one out of ten mice treated with the anti-CD40 antibody alone were tumor free (Ramos lymphoma) while ten out of ten mice treated with the combination of the anti-CD40

antibody and the anti-CD20 antibody were tumor free (Ramos lymphoma). In view of the references cited by the Examiner, this non-cumulative effect shown in Example I was surprising and unexpected.

In view of the above, Applicant respectfully submits that the Examiner has not established a prima facie case of obviousness, and claims are not obvious over the references cited by the Examiner. Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

In response to applicant's arguments against the references individually, one cannot show non - obviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

In response to applicant's arguments that there is no prima facie case of obviousness to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the prior art does teach treating neoplastic diseases with anti-CD40 antibodies and anti-CD20 antibodies, including their combination

While applicant focuses on the mechanism of action of the instant anti-CD40 S2C6 antibody and the anti-CD40 antibodies employed in the prior art,
the prior art does teach administering the instant anti-CD40 S2C6 antibody to treat neoplastic diseases and
the prior does teach the combination of anti-CD40 antibodies and anti-CD20 antibodies in the treatment of neoplastic diseases at the time the invention was made.

In addition to the teachings above, it was known and practiced at the time the invention was made that the use of cancer therapy relies upon a number of basic principles, including combination therapy wherein different agents are used and can be directed at a different molecular target.

While applicant focuses on the issues that known anti-CD40 antibodies at the time the invention was made acted via different mechanisms,
Applicant ignores that the prior art art does teach administering the instant anti-CD40 S2C6 antibody to treat neoplastic diseases and
the prior does teach the combination of anti-CD40 antibodies and anti-CD20 antibodies in the treatment of neoplastic diseases at the time the invention was made.

In this case the teachings of the prior art indicated success in administering the instant anti-CD40 S2C6 antibody to treat neoplastic diseases and the prior does teach the combination of anti-CD40 antibodies and anti-CD20 antibodies in the treatment of neoplastic diseases at the time the invention was made in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

With respect to applicant's reliance upon unexpected results based upon the Examples in the instant specification,

it is noted that applicant relies upon results based upon an certain parameters under certain experimental conditions of an experimental model of cancer, wherein such models may be / can be helpful in analysis, such models have been known not to be predictive of therapy in humans,

it is noted that these experimental models rely upon the administration of antibodies at or nearly at the time of inoculating tumor cells, which is not the normal course of cancer therapeutic regimens, which occur after cancer is diagnosed.

Further, it does not appear that the instant Examples differ from the prior art teachings of treating neoplastic diseases by targeting two different molecular targets of CD40 and CD20 at the time the invention was made.

Also, it is noted that it appears that the Experimental model compared anti-CD40 antibody or anti-CD20 antibody alone in comparison to the combination of anti-CD40 antibody and anti-CD20 antibody.

However, it appears that the Experimental model does not compare two doses of either anti-CD40 antibody or anti-CD20 antibody as a control of providing the same amount of therapeutic antibodies in comparison to the combination of anti-CD40 antibody and anti-CD20 antibody.

In the Experimental model, the combination of anti-CD40 antibody and anti-CD20 antibody resulted in animals receiving twice the amount of therapeutic antibody in comparison to receiving anti-CD40 antibody or anti-CD20 antibody.

Here, the asserted unexpected results do not appear unexpected nor commensurate in scope with the claimed invention.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (e.g, anti-CD40 antibodies and anti-CD20 antibodies in the treatment of neoplastic diseases) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (administering anti-CD40 antibodies and anti-CD20 antibodies in the treatment of neoplastic diseases) with no change in their respective functions and the combination would have yielded nothing more than predictable results of treating neoplastic diseases with the combination of anti-CD40 antibodies and anti-CD20 antibodies in the treatment of neoplastic diseases.

The rationale to support a conclusion that the claims would have been obvious is that a methods of anti-CD40 antibodies and/or anti-CD20 antibodies in the treatment of neoplastic diseases was made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known methods of treating neoplastic diesases by administering anti-CD40 antibodies and/or anti-CD20 antibodies would have been predictable to one of ordinary skill in the art at the time the invention was made.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (administering anti-CD40 antibodies and/or anti-CD20 antibodies in the treatment of neoplastic diseases) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying these known techniques, including known and practiced techniques of targeting different molecular targets with different agents in cancer therapeutic regimens that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (to administer anti-CD40 antibodies and/or anti-CD20 antibodies in the treatment of neoplastic diseases and combination therapy encompassing targeting different molecular targets with different agents) within his or her technical grasp. This leads to the anticipated success of treating neoplastic diseases anti-CD40 antibodies and anti-CD20 antibodies. It is likely the product not of innovation but of ordinary skill and common sense.

With respect to newly added claims, 56-57, Siegall et al. teach S2C6 antibodies, derivatives and analogs that describe substitutions encompass by the claimed invention (e.g., see Detailed Descriptoin, including columns 7-21).

The following is reiterated for applicant's convenience.

Siegall teach methods of treating cancer, including leukemias, lymphomas (e.g. non-Hodgkins lymphoma), solid tumor and multiple myeloma (e.g. see Therapeutic Uses, including Table 1 on columns 22-23 and Claims) with CD40-specific antibodies, including the S2C6 CD40-specific antibody of the instant invention (see entire document, including Claims)

Siegall differs from the claimed methods by not disclosing the known use of combination therapy in the treatment of neoplastic diseases or disorders, including the use of anti-CD20 antibodies in the treatment of such neoplastic diseases or disorders.

Li et al. teach the well known use of combination therapy in the treatment of such neoplastic diseases or disorders (e.g., columns 86-),
including leukemias, lymphomas and multiple myeloma as the elected species (e.g., columns 102 and column 151),
including Rituximab / anti-CD20 antibodies (see column 147, paragraph 3)
and anti-CD40 antibodies, including agonistic antibodies (e.g., see column 3, paragraph 3)
Grillo-Lopez teach treating various tumors with CD20-specific antibodies, including Rituixmab (see columns 5-8 (see entire document) and teachings the expression of CD20 on multiple myeloma (e.g. see columns 15-16, overlapping paragraph) in addition to leukemias and lymphomas (e.g. see Field of the Invention on column 1 and Detailed Description of the Invention and Claims).

Benoit et al. provides additional motivation of combining anti-CD40 antibodies with anti-CD20 antibodies in the treatment of B cell lymphomas.
Benoit et al. teach the increased inhibition of proliferation of B cell lymphomas following litigation of CD40, and CD20, for example (see entire document, including Abstact and Discussion).

Given both the therapeutic use of CD40-specific antibodies and CD20-specific antibodies to treat various neoplastic diseases, including leukemias, lymphomas, myelomas and solid tumors, the ordinary artisan would have been motivated to combine the two antibody specificities in combination therapies to target other neoplastic tissues in order to increase the efficacy of cancer treatment. As taught by all of the prior art references, combination therapies, including combination with antibodies or combination of antibodies with more traditional chemotherapy and radiotherapy were well known and practiced by the ordinary artisan at the time the invention was made to increase efficacy of treatment and to minimize toxic effects of such treatment in order to meet the needs of the patients (e.g., see Detailed Descriptions of Siegall and Grillo-Lopez). The claimed recombinant antibodies and antigen-binding fragments were well known and employed at the time the invention was made. Modes of administration (e.g. simultaneously and sequentially) were practiced by the ordinary artisan as standard regimens in meeting the needs of the patient at the time the invention was made.

In this case the teachings of the prior art do provide for the use of anti-CD40 antibodies in the treatment of certain neoplastic disorders and diseases and do indicate success in treating neoplastic disorders and diseases with anti-CD40 antibodies in combination with anti-CD20 antibodies that would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the combination of the prior art disclosure in motivating the ordinary artisan to administer anti-CD20 antibodies and anti-CD40 antibodies to treat patients with neoplastic diseases or conditions.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to treat patients with neoplastic diseases or conditions with anti-CD20 antibodies and anti-CD40 antibodies,
incorporating the combination of anti-CD20 antibodies and anti-CD40 antibodies in therapeutic regimens with patients with neoplastic diseases or disorders would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such therapeutic methods to treat said neoplastic diseases and disorders.

Applicant's arguments have not been found persuasive.

7. Claims 1-8, 14-15, 32-33, 36-39, 46-52 and 55-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 and 31-53 of copending USSN 11/537,559.

The instant and copending claims appear to be drawn to the same or nearly the same methods of treating neoplastic diseases or disorders (including non-elected species) with the same or nearly the same CD40-specific antibodies and CD20-specific antibodies. Therefore, the copending claims and the instant claims appear to anticipate or render obvious one another.

Applicant's request, filed 01/07/2009, that the rejection be held in abeyance until allowable subject matter is indicated in this or the copending application is acknowledged.

However, the obviousness-type double patenting is deemed appropriate and is maintained for the reasons of record.

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
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